Safety and Efficacy of First-Line Bevacizumab with Chemotherapy in Asian Patients with Advanced Nonsquamous NSCLC

Results from the Phase IV MO19390 (SAiL) Study

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Introduction: First-line treatment with bevacizumab combined with chemotherapy has been shown to improve outcomes in patients with advanced, nonsquamous non-small cell lung cancer (NSNSCLC) in phase III clinical trials. SAiL (MO19390), an open-label, multicenter, single-arm study, evaluated the safety and efficacy of first-line bevacizumab-based treatment in clinical practice. This report presents the results of a preplanned subanalysis of Asian patients enrolled in SAiL.

Methods: Patients with untreated, locally advanced, metastatic or recurrent NSNSCLC received bevacizumab 7.5 or 15 mg/kg every 3 weeks plus chemotherapy for up to six cycles, followed by single-agent bevacizumab until disease progression. Eligibility criteria for SAiL permitted enrolment of a broad patient population. The primary end point was safety; secondary end points included time to disease progression and overall survival.

Results: The Asian intent-to-treat population comprised 314 of the 2212 patients enrolled in the SAiL trial. In the Asian subanalysis, patients received a median of nine cycles of bevacizumab, and the median follow-up was 16.4 months. The incidence of clinically significant adverse events (grade ≥3) of special interest was relatively low in this population (15.6% overall); proteinuria (7.6%), hypertension (4.8%), and bleeding (2.5%) were the most common. A total of five adverse events related to bevacizumab were reported as grade 5. Disease control rate was 94.1%, median time to disease progression was 8.3 months, and median overall survival was 18.9 months.

Conclusions: The safety and efficacy of first-line bevacizumab-based treatment in Asian patients with advanced NSNSCLC is consistent with that demonstrated in phase III studies and in the overall SAiL population. There were no new safety signals.

Key Words: Asian Continental Ancestry Group, Bevacizumab, Chemotherapy, Non-small cell lung cancer.

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Lung cancer imposes a considerable public health and economic burden in Asian countries. In mainland China, for example, the incidence of lung cancer has increased rapidly over the past 2 decades, especially in females.[1] In 2005, there were 497,908 new cases and 428,936 deaths in China, the highest values for any malignancy.[2] Ten-year relative survival for lung cancer from the Singapore Cancer Registry was 5.2% in men and 7.2% in women for the years 1998–2002, with only pancreas and liver cancers having similar or lower survival rates.

Smoking rates and habits have a primary influence on lung cancer incidence in Asian countries, and smoking rates are ominously high, particularly among Asian men.[3] Approximately two-thirds of adult Chinese men are smokers,[4] and with smoking rates increasing and yet to peak in China and other developing countries, deaths due to lung cancer are expected to reflect this situation in the future. However, risk factors for lung cancer vary among local population groups and can include ambient urban air pollution as well as occupational exposures such as cooking fumes. Finally, despite the importance of smoking and environmental pollutants, it is notable that never smokers with non-small cell lung cancer are found disproportionately high in Asian patients, particularly females with adenocarcinoma.

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With an urgent need for therapies that offer improved outcomes and mitigate the burden of lung cancer, intensive research efforts are aimed at developing novel treatment strategies. Bevacizumab is a targeted antivascular endothelial growth factor therapy that produces antitumor effects via inhibition of angiogenesis and is indicated in several tumor types, including nonsquamous non-small cell lung cancer (NSNSCLC), metastatic colorectal cancer, metastatic breast cancer, advanced and/or metastatic renal cell cancer, and glioblastoma multiforme. The benefit of bevacizumab in combination with standard platinum-based chemotherapy as first-line treatment of unresectable, locally advanced, recurrent or metastatic NSNSCLC has been established in two randomized phase III studies, the Eastern Cooperative Oncology Group 4599 (E4599)[5] and Avastin in Lung (AVAiL; BO17704).[6] In E4599, first-line bevacizumab in combination with carboplatin/paclitaxel, followed by single-agent bevacizumab until disease progression, increased the overall survival (OS) in the overall population to 12.3 versus 10.3 months achieved with chemotherapy alone (hazard ratio [HR] = 0.79; $p = 0.003$). Median progression-free survival (PFS) was also increased from 4.5 to 6.2 months with the addition of bevacizumab (HR = 0.66; $p < 0.001$). In the AVAiL trial, PFS was significantly prolonged in the patient population receiving bevacizumab-based therapy compared with chemotherapy alone (median PFS, 6.7 versus 6.1 months; HR = 0.75; $p = 0.003$ in the 7.5 mg/kg bevacizumab group and 0.65 versus 6.1 months; HR = 0.82; $p = 0.03$ in the 15 mg/kg bevacizumab group). The median OS in AVAiL was longer than 13 months in all treatment groups, the improvement with the addition of bevacizumab was not statistically significant compared with chemotherapy alone (7.5 mg/kg group: HR = 0.93; $p = 0.420$; 15 mg/kg group: HR = 1.03; $p = 0.761$).

Thus far, cost and risk benefit are controversial issues around the use of bevacizumab in daily practice. Although there are several economic analyses in a number of countries that evaluate the costs of NSCLC treatments,[7] only a few are available for novel targeted therapies such as bevacizumab. Several recent publications have reported the findings of analyses on the cost-effectiveness of first-line treatment with bevacizumab plus cisplatin and gemcitabine compared with pemetrexed plus cisplatin from Italy and Germany in advanced NSNSCLC, with the direct costs for drug acquisition and administration taken into account. The clinical benefits with bevacizumab appeared to be achieved at a lower monthly cost than the chemotherapy doublet regimen for these patient populations. However, as with any study, one must bear in mind the limitations of the analysis, the principal one being the lack of direct comparisons between treatment regimens.[8,9]

The recently completed SAiL trial (MO19390) aimed to provide further data on the safety and efficacy of bevacizumab combined with a range of standard first-line chemotherapy regimens in a broad patient population with advanced or recurrent NSNSCLC, reflecting clinical practice in the community setting. In the overall SAiL cohort ($n = 2212$), the incidence of grade 3 or higher adverse events (AEs) of special interest was low (3.6%, 5.7%, and 3.0% for bleeding, hypertension, and proteinuria, respectively), and bevacizumab regimens produced highly favorable outcomes, as reflected in disease control rate (DCR; 88.7%), median time to disease progression (TTP; 7.8 months), and median OS (14.6 months).[10]

Knowing that the response to targeted therapies may vary among ethnic populations,[11–14] we report the results of a preplanned analysis of SAiL data for Asian patients (from the source countries China, Taiwan, and Hong Kong). Findings from this analysis will be placed in context with those of phase III studies conducted primarily in Caucasian populations with advanced NSNSCLC (E4599 and AVAiL).

PATIENTS AND METHODS

Study Objectives

The primary objective of this preplanned subanalysis of the SAiL study was to evaluate the safety profile of bevacizumab when combined with chemotherapy in the first-line treatment of patients of Asian origin with locally advanced, recurrent or metastatic NSNSCLC. Secondary objectives were to evaluate the efficacy of bevacizumab, in terms of TTP and OS, and to assess the safety of bevacizumab combinations in patients developing central nervous system (CNS) metastases.

Patient Population

The Asian subpopulation included patients recruited from centers in China (nine sites), Hong Kong (six sites), and Taiwan (five sites). Key inclusion criteria were histologically or cytologically documented, inoperable, locally advanced (stage IIIB with supraclavicular lymph node metastases or malignant pleural or pericardial effusion), metastatic (stage IV) or recurrent NSNSCLC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0 to 2; life expectancy ≥3 months; and adequate hematological, hepatic, and renal function. Patients recruited from China had to have ECOG PS 0 to 1. Key exclusion criteria included mixed, non-small cell, and small cell tumors or mixed adenosquamous carcinomas with a predominant squamous component; history of hemoptysis (≥2.5 ml red blood per episode) within 3 months before enrolment; radiological evidence of tumor invading or abutting major blood vessels; evidence of CNS metastases (even if previously treated); neoadjuvant or adjuvant chemotherapy within 6 months before enrolment; major surgery within 28 days before enrolment; uncontrolled hypertension, thrombotic, or hemorrhagic disorders; and radiotherapy with curative intent within 28 days before enrolment. Patients on full-dose anticoagulation were also excluded.

Study Design and Treatment

Eligible patients received bevacizumab at a dose of either 7.5 or 15 mg/kg every 3 weeks (at the investigator's discretion) for up to six cycles, in combination with standard first-line chemotherapy (selected at the investigator's discretion). In the absence of disease progression, patients continued to receive single-agent bevacizumab treatment until the development of progression or unacceptable toxicity. Patients recruited from China received bevacizumab at a dose of 15

mg/kg combined with carboplatin (AUC 6 every 3 weeks) and paclitaxel (175 mg/m^2 every 3 weeks).

Safety Analysis

The safety profile of first-line bevacizumab combined with chemotherapy was assessed from incidence data for all reported serious AEs (SAEs) and non-SAEs. The incidence of several AEs of special interest was also noted: hypertension, proteinuria, wound healing complications, gastrointestinal perforations, arterial and venous thromboembolic events, hemoptysis, CNS bleeding, other hemorrhages, and congestive heart failure.

National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 was used to classify the severity of AEs. All AE data were recorded up to 28 days after the last bevacizumab infusion, whereas AEs of special interest were reported up to 6 months after the last bevacizumab dose. Bevacizumab-associated SAEs were reported for the duration of the study.

Efficacy Analysis

Duration of survival was defined as the time period from the start of first-line therapy to death. Where the date of death was missing, the most recent date at which the patient was known to be alive was used. Patients with no death recorded at the time of analysis were censored at the most recent date that they were known to be alive. Tumor assessments were performed according to the treating physicians' clinical practice; no specific evaluation method or frequency was protocol-mandated, and no centralized independent evaluation was conducted.

TTP was defined as the time period from the start of first-line therapy to investigator-assessed disease progression. Where the date of progressive disease (PD) was missing, the date of the respective visit was used. Patients who had not progressed at the time of the analysis, including patients who died before PD, were censored at the date of last bevacizumab administration. Information on treatment used after disease progression was not collected.

This report presents data for the efficacy and safety of first-line bevacizumab-based therapy in Asian patients enrolled in SAiL, with a final date for inclusion of July 24, 2009.

Statistical Analysis

This primary population for this subanalysis was the subset of the intent-to-treat (ITT) population of SAiL enrolled from China, Hong Kong, and Taiwan with at least one valid postbaseline assessment. Statistical methods were those used in the overall SAiL population analyses; analyses of demographics, baseline characteristics, safety, and efficacy were based on this population. Estimated 95% confidence intervals (CIs) and event rates were calculated. The incidence of infrequent ($\leq$1%) SAEs were estimated within approximately -0.4% to $+0.5\%$ (for the overall study population), and the incidence of uncommon SAEs was estimated to within approximately -1.7% to $+2.3\%$ (for any subpopulation of 500 patients). SAEs were summarized by incidence rates and 95% Pearson-Clopper CIs. Incidence rates and 95% Pearson-Clopper CIs were also produced for AEs of special interest, including all events regardless of severity or relationship to bevacizumab treatment.

RESULTS

Patients and Treatments

The ITT population in this analysis comprised 314 patients of Asian ethnicity, recruited from China (n = 197), Hong Kong (n = 55), and Taiwan (n = 62) between August 2006 and June 2008. Demographic data for the study population are summarized in Table 1. Patients had a mean age of 55.5 years, 56.4% were male, and approximately one-half were current or former smokers. The majority of patients (70.7%) had stage IV disease at entry, and 69.1% had an ECOG PS of 1. Among those with tumor sampling (97.8%), adenocarcinoma was present in 95.1%. A total of 153 patients (48.7%) were receiving medications at baseline, with 50 (15.9%) receiving cardiovascular medication, 66 (21.0%) receiving analgesics, 70 (22.3%) being treated for hyperten-

TABLE 1. Summary of Demographic and Baseline Characteristics for the SAiL Asian Population

Parameter	SAiL Asian Population (n = 314)
Age, yr, mean (range)	55.5 (25–78)
Male, *n* (%)	177 (56.4)
ECOG PS, *n* (%)	
0	88 (28.0)
1	217 (69.1)
2	9 (2.9)
Smoking status, *n* (%)	
Never	161 (51.3)
Former	122 (38.9)
Current	31 (9.9)
Stage, *n* (%)	
IIIb	92 (29.3)
IV	222 (70.7)
Metastatic site, *n* (%)[a]	
Bone	96 (43.0)
Lung	149 (66.8)
Liver	22 (9.9)
Other	57 (25.6)
Pathology, *n* (%)[b]	
Adenocarcinoma	292 (95.1)
Bronchoalveolar carcinoma	4 (1.3)
Large cell carcinoma	1 (0.3)
Other	10 (3.3)
Centrally located lung cancer, *n* (%)	67 (21.3)
Tumor cavitated, *n* (%)	10 (3.2)
Receiving baseline medication, *n* (%)	
Cardiovascular	50 (15.9)
Analgesics	66 (21.0)
Anticoagulants (prophylactic)	1 (0.3)

[a] Percentages based on patients with metastatic disease; multiple entries were possible.
[b] Percentages based on patients with tumor samples taken (97.8% of total).
ECOG PS, Eastern Cooperative Oncology Group performance status.

sion, and a single patient receiving prophylactic anticoagulant treatment.

Patients received bevacizumab at a dose of 15 mg/kg (n = 310; 98.7%) or 7.5 mg/kg (n = 4; 1.3%). Patients received a median of nine cycles of bevacizumab (range, 1–38) and six cycles of chemotherapy (range, 1–9), and the median duration of follow-up in this population was 16.4 months. The median duration of bevacizumab treatment was 27.3 weeks and that of chemotherapy was 15.1 weeks. The number of cycles of bevacizumab received was between 1 and <4 in 43 patients (13.7%), 4 and <7 in 59 (18.8%), 7 and <10 in 61 patients (19.4%), and ≥10 in 151 (48.1%). Bevacizumab was most commonly combined with carboplatin doublet chemotherapy regimens (76.1%) and more specifically carboplatin/paclitaxel (63.7%). Cisplatin doublets were administered to 18.8% of patients and in nearly all cases cisplatin was combined with gemcitabine (18.2%). Monotherapy regimens were administered to 0.6% of the population, and 4.5% of patients switched chemotherapy regimens during the study.

Safety and Tolerability

AEs of special interest (all grades) were reported in 74.8% of patients, the most common being proteinuria, hypertension, and bleeding (Table 2). Ninety-two SAEs occurred in 61 patients (19.4%), of which 17 in 15 patients (4.8%) were deemed by investigators to be related to bevacizumab treatment. However, the incidence of clinically significant (grade ≥3) AEs of special interest was only 15.6%. The most common clinically significant AEs of special interest were proteinuria (experienced by 7.6% of patients) and hypertension (experienced by 4.8% of patients).

Despite 43 patients developing CNS metastases during study treatment, only three (grade 1) CNS bleeding events were reported. There were no instances of grade ≥3 wound healing complications, and congestive heart failure was not observed during the study. Five grade 5 AEs were reported: hemoptysis, pulmonary embolism, cerebral infarction, lacunar infarction, and acute hepatitis. Most (76.6%) of AEs of special interest resolved or improved during the study (Table

TABLE 2. Incidence of Adverse Events of Special Interest According to CTC Grade in the SAiL Asian Population

	SAiL Asian Population (n = 314)						
	All Grades	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Grade ≥3**
Bleeding	49.7	44.3	7.6	2.2	0	0.3	2.5
Epistaxis	36.9	34.1	3.2	1.0	0	0	1.0
Pulmonary hemorrhage[a]	13.4	10.8	1.9	0.3	0	0.3	0.6
CNS bleeding[b]	1.0	1.0	0	0	0	0	0
Other bleeding	14.0	11.5	2.5	1.0	0	0	1.0
Hypertension	29.3	12.7	16.2	4.8	0	0	4.8
Proteinuria	40.4	17.8	22.0	6.4	1.3	0	7.6
Thromboembolic events	3.2	0.3	1.0	0.6	1.0	1.9	2.2
Gastrointestinal perforation	0.6	0	0	0.3	0.3	0	0.6
Wound healing complications	0.6	0.3	0.3	0	0	0	0

Values are given as percentage of patients.
[a] Pulmonary hemorrhage/hemoptysis.
[b] Cerebral hemorrhage/hematoma.
CTC, common toxicity criteria; CNS, central nervous system.

TABLE 3. Adverse Events (AEs) of Special Interest by Outcome and Action Taken (Based on Total of 649 AEs in the Asian Population; n = 314)

	Outcome				Action Taken	
AEs, n (%)[a]	**Resolved**	**Improved**	**Persistent**	**Led to Death**	**Temporarily Interrupted**	**Permanently Discontinued**
Any AE (n = 649)	433 (66.7)	64 (9.9)	148 (22.8)	4 (0.6)	28 (4.3)	32 (4.9)
Bleeding (n = 299)	258 (86.3)	13 (4.3)	27 (9.0)	1 (0.3)	3 (1.0)	17 (5.7)
Hypertension (n = 126)	61 (48.4)	18 (14.3)	47 (37.3)	0 (0.0)	15 (11.9)	2 (1.6)
Proteinuria (n = 208)	109 (52.4)	29 (13.9)	70 (33.7)	0 (0.0)	9 (4.3)	5 (2.4)
Thromboembolism (n = 12)	2 (16.7)	3 (25.0)	4 (33.3)	3 (25.0)	1 (8.3)	6 (50.0)
Gastrointestinal perforation (n = 2)	1 (50.0)	1 (50.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (100.0)
Wound healing complications (n = 2)	2 (100)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Total number of AEs = 649.
[a] Percentages are based on total number of AEs within each AE category.

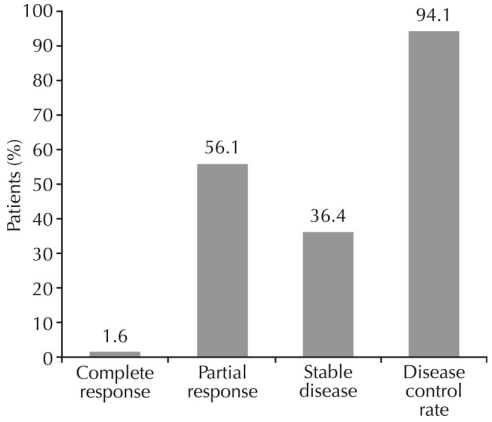

FIGURE 1. Efficacy outcomes based on tumor assessment in the SAiL Asian population ($n = 305$).

3). Interruption or permanent discontinuation of bevacizumab administration because of AEs of special interest was an infrequent occurrence (9.2%; Table 3).

Clinical Efficacy

Efficacy was evaluable in 305 of the 314 patients in the ITT population (97.1%). In these patients, the overall response rate was 57.7% and the DCR was 94.1% (Figure 1). At the final efficacy analysis of the ITT population, 241 patients (76.8%) had experienced PD; 73 patients had not progressed or had died before PD and were censored. The median TTP determined by Kaplan-Meier analysis was 8.3 months (95% CI: 7.7–8.8) at a median follow-up of 16.4 months (Figure 2). During the period for which data were analyzed, 162 patients (51.6% of the ITT population) died, 153 (94.4%) of them from lung cancer. Median OS was 18.9 months (95% CI: 17.4–20.7), based on 152 censored patients.

DISCUSSION

The SAiL trial, a multicenter single-arm investigation involving 400 centers worldwide, assessed the safety and efficacy profile of first-line bevacizumab therapy in a broad population of more than 2000 patients with advanced NSNSCLC.[10] The results from a preplanned subanalysis of Asian patients are consistent with those of the overall SAiL population.

The safety analysis of the global SAiL population showed a generally low incidence of grade ≥3 AEs of special interest to bevacizumab, such as bleeding (3.6%), hypertension (5.7%), proteinuria (3.0%), thromboembolism (7.8%), congestive heart failure (0.5%), and gastrointestinal perforation (1.2%). The comparative rates for these grade ≥3 AEs in the SAiL Asian population were similarly low: 2.5%, 4.8%, 7.6%, 2.2%, 0%, and 0.6%, respectively, and no new safety signals related to bevacizumab were reported in this population. The above rates for the SAiL Asian subpopulation were also consistent with those reported in phase III, randomized, controlled trials of bevacizumab combined with chemotherapy in advanced NSNSCLC (E4599[5] and AVAiL[6]) and with the phase II Japanese trial JO19907.[10]

Efficacy data from this subanalysis, albeit positive, should be interpreted with caution, given that SAiL was a single-arm study and the tumor assessments were performed according to the physicians' clinical practice (DCR of 94.1%, median TTP of 8.3 months, and median OS of 18.9 months for bevacizumab-treated patients). In the overall SAiL population, DCR was 89%, the median TTP was 7.8 months, and the median OS was 14.6 months.[10] In bevacizumab-treated patients in the E4599 trial, median PFS was 6.2 months, and in AVAiL, it was 6.7 and 6.5 months,[12] for the 7.5 and 15 mg/kg bevacizumab groups, respectively. Median OS was longer than a year in both E4599 and AVAiL (E4599: 12.3 months[5]; AVAiL: 13.6 and 13.4 months[15] for the 7.5 and 15 mg/kg groups, respectively). Patients with adenocarcinoma histology in E4599 reached a median OS of 14.2 months.[16]

A post hoc analysis of efficacy data from a small cohort ($n = 105$) of Asian patients in AVAiL supports an enhanced benefit in this subgroup compared with the overall study population (unpublished observation). Bevacizumab 7.5 and 15 mg/kg versus chemotherapy alone prolonged PFS to 8.8 months (HR 0.49) and 8.7 months (HR 0.61 versus 6.1 months) and increased overall response rate (47% and 41% versus 15%) and median OS (28 months [HR 0.46] and 26 months [HR 0.79] versus 17.4 months), respectively. In addition, a randomized study of 180 Japanese patients with

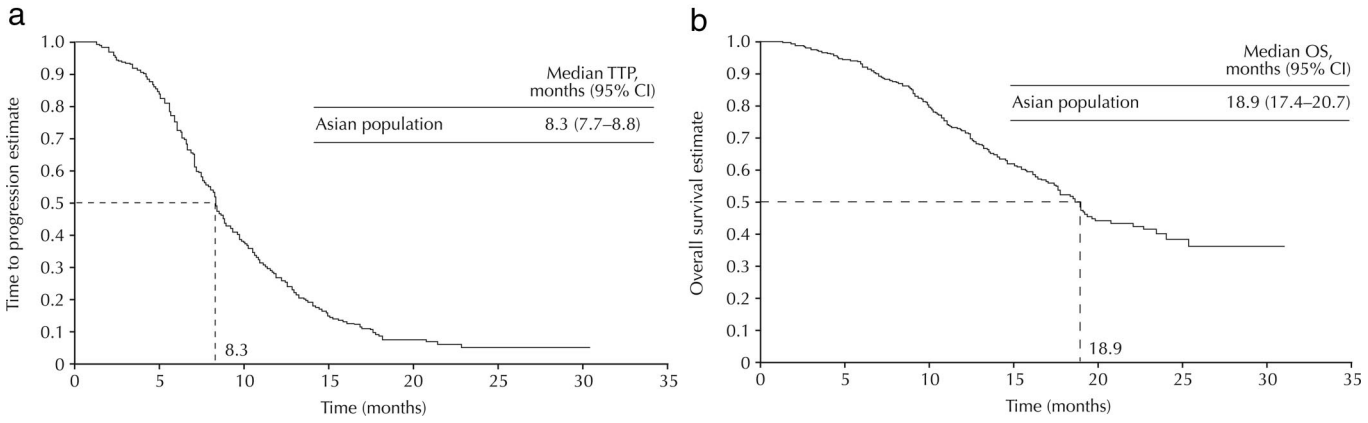

FIGURE 2. Median time to disease progression (*a*) and median overall survival (*b*) in the SAiL Asian population.

advanced NSNSCLC (JO19907) demonstrated that the addition of bevacizumab to carboplatin doublet therapy significantly prolonged median PFS (6.9 versus 5.9 months; $p = 0.009$) and substantially increased overall response rate (61% versus 31%; $p = 0.0013$) and DCR (94% versus 71%; $p = 0.0002$), compared with chemotherapy alone.[14]

Efficacy data for bevacizumab in Asian patients suggest an enhanced benefit in this NSNSCLC subpopulation compared with data from trials conducted in mainly Caucasian populations; the same is noted for clinical trials involving chemotherapy[17] or epidermal growth factor receptor tyrosine kinase inhibitors (regardless of epidermal growth factor receptor mutational status).[12–21] It is also worth noting that, for reasons that remain uncertain, adenocarcinoma histology appears to be more treatment-responsive and its incidence in Chinese patients is among the highest worldwide.[18] Asian patients in SAiL had a greater proportion of never smokers (51% versus 30%) and patients who had adenocarcinoma histology (95% versus 86%) compared with the overall SAiL study group. Although these demographic factors might have contributed to a better outcome, the higher number of Asian patients receiving cardiovascular medication (32% versus 16%) and having a worse ECOG PS profile (ECOG PS 1: 69.1% versus 56.6%) would suggest that there was no bias toward an overall better performing population.

The main limitation of the Asian subanalysis of the SAiL trial is the relatively small number of patients, which reduces the robustness of the study data and does not allow for the reporting of certain key data such as use of bevacizumab with a range of chemotherapy regimens. As noted in the overall SAiL results,[10] the effects of subsequent lines of therapy could not be determined, as these data were not collected. This may have had a confounding effect on the apparent benefit of bevacizumab-based treatment. Clearly, the lack of any control group is also a limitation, although this is a reflection of the clinical setting of a study that aimed to evaluate bevacizumab in everyday oncological practice.

In summary, the safety and efficacy of first-line bevacizumab in combination with chemotherapy was confirmed in this preplanned subanalysis of Asian patients with advanced NSNSCLC enrolled in the SAiL study. In evaluating patients typically seen in clinical practice in the community setting, the SAiL study builds on the experience gained in earlier trials of bevacizumab in more selected groups of patients with NSNSCLC. The findings of this report are consistent with those of the global SAiL population and phase III trials of bevacizumab in this setting. No new safety concerns were identified in the Asian population.

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